INTERNATIONAL GENERIC PHARMACEUTICAL ALLIANCE

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(Letter & response only by fax; complete original package by courier)

November 3, 1999

Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
ROCKVILLE, MD 20852

FAX NO: 301-827-6870

Re: Docket No. 99D-2729

Dear Sir:

Enclosed is a document that has been prepared on behalf of the International Generic Pharmaceutical Alliance (IGPA) in response to the draft Guidance for Industry *"BA and BE Studies for Orally Administered Drug Products – General Considerations"*.

This Draft Guidance, although more general than the Draft Guidance for Industry *"Average, Population, and Individual Approaches to Establishing Bioequivalence"*, incorporates some of the same elements from that Guidance. Specifically, matters pertaining to replicate design and to individual bioequivalence are common to both documents. We will not duplicate the comments on these two topics. However, they are just as critical for consideration in this Guidance as they are for the Guidance on population and individual bioequivalence. Therefore, we ask that you cross-reference the response on population and individual bioequivalence to this General Guidance as well.

Sincerely,

Michael Spino, Pharm.D.,
Chairman, Scientific Affairs Committee, IGPA

MRS/ads
Encl.

99D-2729 C11

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Response to

BA and BE studies for orally administered drug products - general considerations: *DRAFT GUIDANCE*

by

The International Generic Pharmaceutical Alliance (IGPA)

Introduction

The following is a response from IGPA to the Draft Guidance entitled "BA and BE studies for orally administered drug products - general considerations", dated August 1999.

IGPA appreciates the opportunity to comment on the draft because several companies of its member associations (National Association of Pharmaceutical Manufacturers (NAPM), the National Pharmaceutical Association (NPA), the Generic Pharmaceutical Industry Association (GPIA) from the United States, the Canadian Drug Manufacturers Association (CDMA), and the European Generic Association (EGA)) sponsor studies used in ANDA submissions, as part of the data set used to demonstrate safety and efficacy. Some of these associations will make additional presentations to the Agency.

Development of standards, which provide assurance that a brand and generic formulation of the same drug substance are bioequivalent, is an important safeguard for the public. IGPA supports the continuing efforts of the FDA to maintain and improve reasonable testing procedures to provide assurance of comparable safety and efficacy for generic and brand name drugs.

The Scientific Advisory Committee of IGPA has reviewed the Draft Guidance and has considered the proposed principles, procedures, and their applications and provides the following comments for consideration by the FDA.

This Draft Guidance shares elements of commonality with the "Guidance for Industry: Average, Population, and Individual Approaches to Establishing Bioequivalence" (IBE Guidance). In particular, both documents propose the use of replicate designs for bioequivalence studies and advocate the use of individual bioequivalence. Extensive comment has been provided by IGPA to the FDA regarding matters of replicate design and individual bioequivalence (IBE) in response to the IBE Draft Guidance. Although a few comments on these matters will be made in this response, IGPA requests that the FDA refer to the statements on IBE and replicate designs in the IBE Guidance as they have equal relevance to the present Guidance.

General Statement

This "General" Draft Guidance has been issued during a period of time in which several other "specific" Guidances have been issued for comment. Issues addressed in some of these specific Guidances clearly overlap with matters addressed in the General Guidance and as such will need to be considered with them.

In an effort to improve upon some of the perceived deficiencies in Guidances currently being employed in bioequivalence studies, FDA has put forward a number of changes. While some of these changes do appear to lead to a scientifically stronger position, others do not. More importantly, some of the changes introduce extensive modifications that have not been adequately evaluated by the scientific community and warrant a thorough evaluation. While this response provides some comment, it will be necessary to examine some of these proposed changes by employing them in the analysis of actual data before an adequate appreciation of their merit, or lack thereof can be obtained.

Specific Comments

1. Replicate Designs

The Draft Guidance states, "Replicate study designs (see section IV) are recommended for all BE studies using pharmacokinetic measurements, with the following exceptions:...". However, there is absolutely no justification provided for this new recommendation. If it were to be implemented, the cost of conducting BE studies would more than double (data upon which estimate was made are available upon request). If there is a documented need for such a change, cost should not be the determining factor, but in the absence of a demonstrated need, it is unacceptable to introduce such a profound change in the conduct of BE studies.

The only situation that is known to us where there is a requirement for replicate designs, are those related to the conduct of studies designed to evaluate IBE. The strong opposition to IBE expressed over the last few years by the international community of scientists to the FDA proposal on IBE, together with the written proposals in response to this Draft Guidance, and the one on IBE, would lead us to believe that IBE is not likely to be proposed by the FDA as a useful method of conducting and assessing bioequivalence studies. In that case, the need for replicate design studies no longer exists.

One might argue that replicate design studies provide greater opportunity to evaluate data, but that must be weighed against the benefit to be accrued from the additional cost of time and human resources associated with the collection of the additional data generated from replicate design studies. In our opinion, 2 period cross-over studies are cost-effective and provide ample opportunity to

assess the relevant aspects of BE. Expanding the amount of data being requested for BE studies should be mandated only in the presence of clear scientific evidence demonstrating that more data is actually required (nice to know versus need to know).

In the absence of a demonstrated need for conducting replicate design studies, it is imperative that the Agency not indicate to sponsors that replicate designs are recommended or even preferable. Such a statement would lead companies to undertake the additional expense, even if not warranted from a scientific basis, because of their concern that the FDA might not give favorable consideration to their submission unless it were conducted under replicate design conditions.

In some cases, there may be a justification for replicate design studies and in those cases they should be recommended. For example, the Expert Panel has recommended (September 1, 1999 at the AAPS Workshop in Montreal) that replicate designs should be employed in the assessment of modified-release dosage forms during an interim 2 year experimental period. We propose that sponsors also should be able to use such a design if it is evident that BE will be established more readily using a replicate design, as may be the case for some cases of highly variable drugs.

2. Selection of Subjects

On page 8, Secton 5 *Study Population*, an attempt is made to be all inclusive in the selection of subjects, such as including males and females, young and elderly, as well as different racial groups. We believe this approach to be impractical, and unnecessary. It appears to stem mainly from the perspective of IBE and the need to have a disparate group of subjects to pick up potential subject-by-formulation interactions. However, even if this were the case, the number of subjects in any one category most likely would be too small to have statistical significance. Such a requirement would also severely impair the ability of clinics to conduct studies due to regional differences in the population available to study. It is preferable to not have restrictions in the inclusion criteria, but rather let the population of the city where the clinic is located, dictate the make-up of the study population. We do not necessarily object to the inclusion of such subjects, only that their inclusion, if mandated, would perturb the recruiting situation and may even lead to unrealistic expectations about subgroup data analysis.

3. Multiple-Dose Studies

We concur with the view that single-dose studies are generally more sensitive and therefore multiple-dose studies are generally not required. We also agree with the position that multiple-dose studies may be conducted. This is particularly important because there is a need to employ various study designs to

establish BE for some drugs where it is difficult to demonstrate BE with single dose studies.

4. Pharmacokinetic Measures of Systemic Exposure

The Draft Guidance speaks to the limitations of Cmax. While recognizing these limitations, IGPA also considers that the Cmax measure is valuable since it is not an isolated parameter, even though it may be analyzed as such. Cmax, for a given subject, is embraced within the confines of the measured AUC, and as such, embodies a level of definition for that subject. It also has a long history of use within the field of BA and BE and its utility has been well-described, notwithstanding its limitations. Therefore, we concur with FDA in their view that Cmax remain an important regulatory parameter in the assessment of BE.

Far less well-described is the partial area concept and other measures of early systemic exposure. While offering some advantages, they have inherent disadvantages of their own. Although they constitute more time points than the single time point for Cmax, they retain much of, and sometimes more, variability than Cmax itself. The reason for this, in many cases, is GI emptying and other related factors in GI transit.

In those cases where there is a demonstrated need for early exposure comparisons, the Guidance should provide a clear indication of what the BE criterion would be, such as in the case of partial AUC. Based on previous experience with this highly variable metric, we would recommend that there be no 90% confidence interval requirement assigned to this metric, but the ratio should be within 80-125%.

Although there is a perception that comparable early serum concentrations would give greater assurance of therapeutic equivalence, we are aware of only very few drugs where it has been demonstrated that the rate of increase in serum concentrations of an orally administered drug (not sublingual) is a determinant of effect.

We concur with the collection of data to help understand such parameters more closely, but we would strongly object to the implementation of early exposure parameters as criteria for BE at this point in time.

5. Pharmacodynamic Studies

IGPA recognizes that pharmacodynamic endpoints are not normally employed in the assessment of BE when serum drug concentrations can be measured. However, there are times when one might find it more appropriate to measure a relevant pharmacodynamic parameter, integral to a drug's action, as the measure of BE, particularly when there is difficulty in assessing serum drug concentrations.

Therefore, we would advise that the Guidance not state "This approach is usually not applicable to orally administered drug products where the drug is absorbed into the systemic circulation.", but rather, "Sponsors who wish to employ a pharmacodynamic measure for the assessment of BE of orally administered drugs may do so upon appropriate justification."

6. In Vitro Testing

The requirement for three batches to set dissolution specifications for modified releases dosage forms in an ANDA would represent a significant new regulatory burden for the generic industry. There is currently no other requirement for three production batches to be manufactured in FDA Guidances or regulations regarding ANDA products. Evaluation of dissolution data from the single biobatch for the purpose of setting dissolution specifications is theoretically no different than setting other drug product specifications such as assay and impurities from data obtained on a single biobatch.

7. Individual Bioequivalence

As noted earlier, extensive comment on IBE has been provided in response to the Draft Guidance released on this topic, and those comments need to be considered in light of the present Draft Guidance.

8. Scaling

The concept of scaling to the reference product has been accepted by the FDA when studies are conducted under conditions of IBE or PBE. Therefore, in the opinion of IGPA, it is reasonable to apply the same concept to studies conducted under conditions of ABE. The utilization of such a technique would facilitate the approval of highly variable, yet bioequivalent drugs.

9. Immediate-Release Products: Capsules and Tablets-General Recommendations

Considerable debate over the last few years has ensued around narrow therapeutic range drugs (NTR), but we are aware of no data demonstrating the need to reduce the permissible ratio for the point estimate. The proposed BE limit of 90-111% for narrow therapeutic range drugs, in most cases is too tight. While this might be suitable for a drug like warfarin, it would not be suitable with other "NTR" drugs like theophylline. With due consideration to the allowable deviation (USP specification) of potency between batches, one needs to recognize that the current criteria do not pose a health risk. If a change were deemed necessary, and IGPA does not believe that to be the case, then a BE limit of 85-118% might be considered for those drugs where there is truly a need to employ a tighter standard.

An alternate approach has been used by TPP in Canada, where the use of 95% confidence intervals has been recommended.

Notwithstanding the rejection of IBE as a regulatory procedure at this time, IGPA wishes to note that the IBE requirement of reference scaling is already appropriate in tightening the BE limit. The requirement of $\varepsilon_I=0$ (i.e., $\theta_I=1.245$) is unreasonable as any difference in within-product variance and the presence of an apparent S*F interaction could be due to chance, rather than a "bad" test product.

10. Modified-Release Products

The Draft Guidance seems to indicate that delayed-release products need to be subjected to replicate design studies. While IGPA is in agreement with the recommendation of conducting replicate design studies on modified-release products for a 2 year interim period, we do not concur with the need to apply this same level of study for products that are modified-release solely on the basis of the fact that they have a lag time, because in other regards, they tend to behave as immediate release products.

A major concern relates to the proposed use of the partial AUC as a criterion for BE of MR products. Such a recommendation is impractical and generally, not clinically relevant. More importantly, it can, depending on the criteria employed and the acceptable range of the confidence interval employed, lead to a non-bioequivalent designation for BE products. Depending on the mechanism for release, GI transit time could easily be much more variable than the formulation and thus the "Cmax" may appear at different times, even for the same product in the same individual on different occasions. The partial AUCs could be greatly different even though the products are identical.

Even today, very few generic MR products are available for compounds such as nifedipine, diltiazem and verapamil using currently recommended BE methods. As has been published in the past for verapamil SR products, the brand compared to itself has a high chance of failing BE assessment using current methodologies. Because partial AUCs are more variable than total AUC, and for many MR products, more variable than Cmax, the application of partial AUC as a criterion, would make it even more difficult to demonstrate bioequivalence-even for identical products. The variability in serum concentrations of MR products is well known and is illustrated in the following figure for the diltiazem brand product sold in Canada. The data were collected as part of a randomized cross-over, two period bioequivalence study. The data in the figure reveal the serum concentrations of only the brand product in each of the subjets. Note: the wide range of Cmax values; the wide range in Tmax; the multiple peaks; and highly variable concentration-time profiles. We suspect that the high level of variability observed among subjects is most likely a function of the variable GI transit time.

Inter-Subject Variaton of Cardizem SR under Fasted Conditions

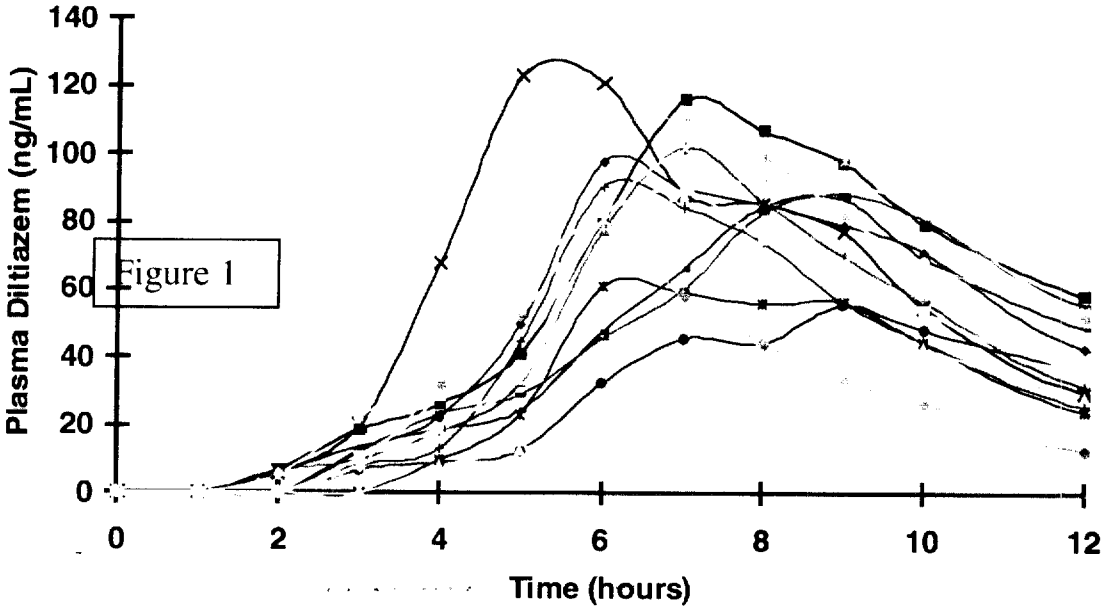
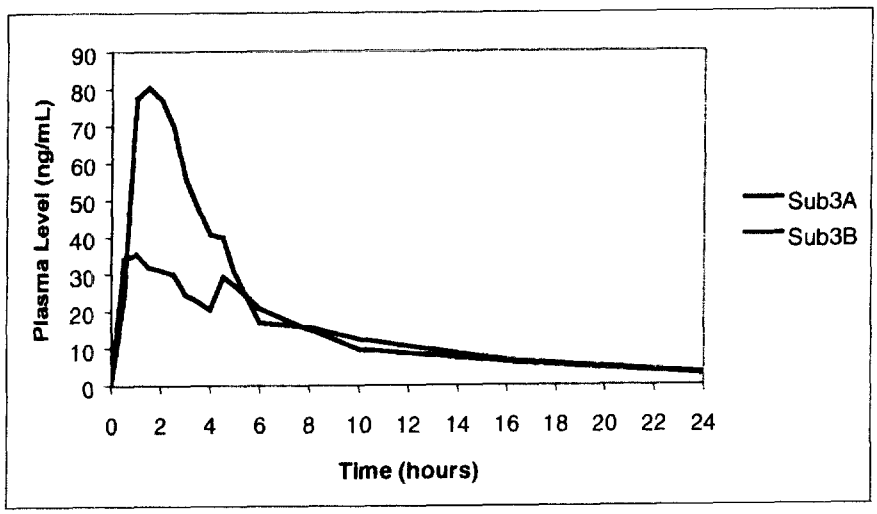
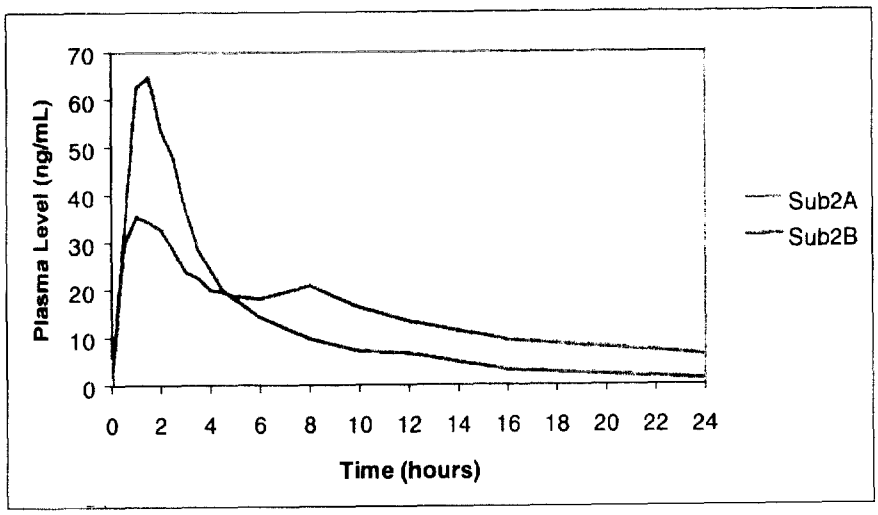


Figure 1

Although the intrasubject differences might be somewhat less than the intersubject differences, individuals also experience highly variable concentrations given the same MR product on different occasions as illustrated in the following examples of 3 individuals given the brand product of nifedipine (Adalat PA 20 mg tablets) at different times. These data were presented on October 4, 1999 at the Drug Dissolution Workshop; Toronto, Canada.


Plasma Level (ng/mL)
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Sub3A
Sub3B


Plasma Level (ng/mL)
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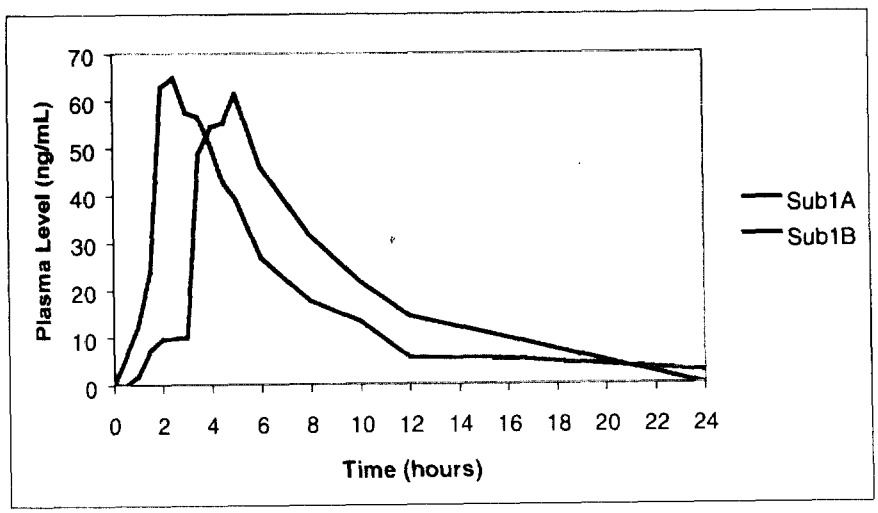
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Sub2A
Sub2B


Plasma Level (ng/mL)
70
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0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Sub1A
Sub1B

From these 2 sets of figures alone, it should be evident that: i) there exists great variability in serum concentrations for MR products both among and within subjects; ii) Tmax occurs over a wide period of time and thus could not have an important clinical correlate for these products; and iii) partial AUCs would be an inappropriate measure for MR products.

The vast majority of MR products are used on a chronic basis and their effects are demonstrated over a 12-24 hour period. We believe that similarity of early exposure is unlikely to be a relevant factor for equivalence in the vast majority of cases as long as total exposure is the same. Based on the variability among subjects seen in Figure 1, this premise should be evident or patients would have inconsistent responses.

For these reasons, the use of early exposure criteria for the assessment of BE of MR products is unwarranted, and may lead to erroneous conclusions regarding a lack of equivalence of identical products.

IGPA would like FDA to reconsider the statement at the bottom of page 16, Section 2 regarding ANDAs: BE Studies. We see no no apparent reason why drugs with nonlinear kinetics should have the same BE limit as with narrow therapeutic range drugs. If the concern is that differences observed with one dose may not be extrapolated to other doses due to nonlinear kinetics, one can choose a clinically relevant dose such that any observed difference in the study represents the maximum difference in BA between the two products. For example, if there is a disproportionate increase in AUC as dose increases, use the maximum recommended dose for the BE study. If the increase in AUC is less than proportional as dose increases, use the lowest dose or lowest strength for the BE study.

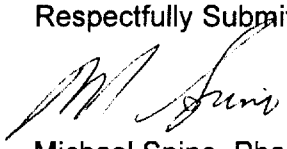
11. Metabolite And Degradant

The approach proposed for dealing with the metabolites in BE studies is clearly one based on science and avoids measurement of unnecessary moieties. However, on page 19, the recommendation for the measurement of serum concentrations of a degradant which may be formed in the lumen of GI tract is a concept that has not been widely discussed and its impact is unknown to us. Our initial thoughts are that it is probably unrealistic. Even if 20% of the dose is converted to the degradant, it is reasonable to assume that not all the degradant will be absorbed. Thus, the level of the degradant in blood may be too low to be measured. The same may also apply to a metabolite that is formed as a result of gut wall or other prehepatic metabolism if less than 20% of the dose is involved. Although FDA has provided some explanation to theoretically support this recommendation, we suggest it needs greater study.

12. Long half-life Drugs

The definition of long half-life may need some consideration. IGPA would propose that drugs with a half-life of >24 hours should be considered for this category. The use of truncation for blood collection has been employed in Canada and the time period for such collection is 72 hours. It would be helpful to obtain from the FDA a suggestion as to what constitutes a suitable truncated blood collection period.

Respectfully Submitted



Michael Spino, Pharm.D
Chairman
Scientific Advisory Committee
IGPA

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